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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,849	06/20/2003	Giovanni M. Pauletti	3715.12-1	8490

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Hana Verny
Peters, Verny, Jones & Schmitt, LLP
Suite 230
425 Sherman Avenue
Palo Alto, CA 94306

EXAMINER	
SCHLIENTZ, NATHAN W	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,849	PAULETTI ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-45* is/are pending in the application.

4a) Of the above claim(s) *43 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-42 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 March 2009 has been entered.

It is noted by the examiner that Applicants did not file Remarks or an amendment to the claims in response to the final office action mailed 26 September 2008, but rather directs attention to the amendment filed 10 June 2008.

Status of Claims

Claims 31-45 are pending in the present application. Claims 43 and 44 withdrawn as being drawn to a non-elected invention. As a result, claims 31-42 and 45 are examined herein on the merits for patentability to the extent they read on the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 31-42 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 31 recites, "wherein said anti-migraine drug is selected from the group consisting of... chlorpromazine, valproic acid, and, and wherein said antinausea...". There should be an "and" between the last two groups in a Markush group (i.e., chlorpromazine, and valproic acid), and it is unclear whether more groups are intended to be listed after valproic acid since there is recited "and, and...".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 31-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et al. (US 6,197,327) in view of Hagenlocher et al. (EP 0 391 852 A2) and Jannetta (US 2002/0055495).

Applicant's claims

Applicants claim a method for a systemic treatment of migraine and migraine headache, nausea and vomiting by delivering a composition comprising an anti-migraine or anti-nausea drug, a lipophilic or hydrophilic carrier, a mucoadhesive agent, and a sorption promoter/penetration enhancer into a systemic circulation with an aid of an intravaginal delivery device, wherein the anti-migraine and anti-nausea drugs are listed in claim 1.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Harrison et al. teach a method for treatment of dysmenorrhea comprising an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrhea (abstract). Harrison et al. further teach the pharmaceutically acceptable carrier comprises a hydrophilic or hydrophobic carrier, such as semi-synthetic glycerides of saturated fatty acids with 8 to 18 carbons and PEG 6000/1500, respectively (column 8, lines 8-15). Also, Harrison et al. teach the pharmaceutical formulations further comprising a mucoadhesive agent, preferably hydroxypropyl methylcellulose (column 8, lines 16-22), and a penetration enhancer, preferably ethoxydiglycol (column 8, lines 23-28). Harrison et al. also teach the method of applying the pharmaceutical formulation with the aid of an intravaginal delivery device, such as tampon device, vaginal ring, pessary, tablet, vaginal suppository, vaginal

sponge, bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam, ointment, solution and gel (column 2, lines 37-43; column 3, lines 8-67; column 4, lines 1-27; and column 9, line 4 through column 13, line 67). Harrison et al. also teach that preferred formulations for hydrophilic drugs comprise between about 60-90% by weight lipophilic carrier, between about 5-25% mucoadhesive agent, and between about 5-20% sorption promoter, whereas preferred formulations for lipophilic drugs comprise between about 50-90% by weight hydrophilic carrier, between about 5-20% mucoadhesive agent, and between about 5-25% sorption promoter (column 8, lines 31-34 and 44-47). Harrison et al. further teach that the drug delivery systems treat or prevent dysmenorrhea, and alleviate and prevent painful menstruation and symptoms such as nausea, fatigue, diarrhea, lower backache, and headache (col. 12, ll. 14-20).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Harrison et al. teach that symptoms such as nausea as a result of dysmenorrhea are treated with their intravaginal drug delivery systems, but they do not teach using the instantly claimed anti-migraine or anti-nausea agents. However, Hagenlocher et al. teach that a plurality of medicines are suitable for rectal or vaginal therapy with the aim of making the medicines absorb systemically or in order to achieve an effect locally in the rectum or the vagina (pg. 2, ll. 3-6). Hagenlocher et al. teach a composition for rectal or vaginal application of drugs comprising at least one hydrocolloid, effective substance(s), and possibly further carrier substances; wherein said compositions are used in systemic or local therapy for rectal or vaginal application (Abstract; pg. 2, ll. 44-

46; and pg. 3, ll. 26). Hagenlocher et al. teach that effective substances include anti-emetic agents, such as metoclopramide, anti-epileptic agents, such as valproic acid, and neuroleptic agents, such as promethazine and chlorpromazine (pg. 3, ll. 30-49); the hydrocolloid includes hydroxypropylmethyl cellulose (pg. 4, ll. 22-37); and carrier substances include polyethylene glycol (pg. 4, ll. 43).

Also, Jannetta teaches suppositories for the treatment of nausea and vomiting, wherein the suppositories are optionally administered in the vagina and comprise metoclopramide ([0013]-[0018]). Jannetta also teaches that the metoclopramide is administered in a dosage of about 10 to about 20 mg twice or thrice a day ([0016]).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to incorporate anti-nausea drugs, such as metoclopramide, into the formulations of Harrison et al., because Hagenlocher et al. teach that vaginal therapy is an effective systemic treatment, and both Hagenlocher et al. and Jannetta teach that anti-nausea drugs can be administered as suppositories.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants do not argue this rejection in their Request for Continued Examination filed 25 March 2009. Therefore, the examiner is responding to Applicant's Remarks filed 10 June 2008.

Applicants argue on page 12 that the aim of Harrison et al. is to deliver the needed amount of the drug to the uterus but limit the concentration of the drug in the systemic circulation. However, the examiner respectfully argues that Harrison et al. teach that the intravaginal delivery results in a reduction of first-pass metabolism in the liver by avoiding the gastrointestinal system, which in turn results in a reduction of side effects due to lower systemic concentrations (col. 5, l. 58 through col. 6, l. 2). The examiner contends that Harrison et al. teach one of ordinary skill in the art that intravaginal administration of a drug bypasses first-pass metabolism in the liver by avoiding the gastrointestinal tract, and therefore has a reduction in side effects. Also, in combination with Hagenlocher et al. and Jannetta, it is obvious that intravaginal delivery of anti-emetic drugs can sufficiently treat nausea. Also, US 6,572,874 teaches intravaginal delivery systems (suppositories) comprising the three basic components: glycerides of saturated fatty acids having eight to eighteen carbons (SUPPOCIRE®), HPMC and ethoxydiglycol (TRANSCUTOL®); wherein the suppositories resulted in systemic circulation of the drug in concentrations ten to thirty times higher than those delivered orally (col. 5, ll. 59-67; and col. 27, ll. 37-43). Therefore, the intravaginal delivery system of Harrison et al. is taught to result in systemic circulation.

2. Claims 31-42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et al. (US 6,197,327) in view of Mahashabde et al. (US 2003/0133977) and Penkler et al. (US 6,255,502).

Applicant's claims

Applicants claim a method for a systemic treatment of migraine and migraine headache, nausea and vomiting by delivering a composition comprising an anti-migraine or anti-nausea drug, a lipophilic or hydrophilic carrier, a mucoadhesive agent, and a sorption promoter/penetration enhancer into a systemic circulation with an aid of an intravaginal delivery device, wherein the anti-migraine and anti-nausea drugs are listed in claim 1.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Harrison et al. teach a method for treatment of dysmenorrhea comprising an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrhea (abstract). Harrison et al. further teach the pharmaceutically acceptable carrier comprises a hydrophilic or hydrophobic carrier, such as semi-synthetic glycerides of saturated fatty acids with 8 to 18 carbons and PEG 6000/1500, respectively (column 8, lines 8-15). Also, Harrison et al. teach the pharmaceutical formulations further comprising a mucoadhesive agent, preferably hydroxypropyl methylcellulose (column 8, lines 16-22), and a penetration enhancer, preferably

ethoxydiglycol (column 8, lines 23-28). Harrison et al. also teach the method of applying the pharmaceutical formulation with the aid of an intravaginal delivery device, such as tampon device, vaginal ring, pessary, tablet, vaginal suppository, vaginal sponge, bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam, ointment, solution and gel (column 2, lines 37-43; column 3, lines 8-67; column 4, lines 1-27; and column 9, line 4 through column 13, line 67). Harrison et al. also teach that preferred formulations for hydrophilic drugs comprise between about 60-90% by weight lipophilic carrier, between about 5-25% mucoadhesive agent, and between about 5-20% sorption promoter, whereas preferred formulations for lipophilic drugs comprise between about 50-90% by weight hydrophilic carrier, between about 5-20% mucoadhesive agent, and between about 5-25% sorption promoter (column 8, lines 31-34 and 44-47). Harrison et al. further teach that the drug delivery systems treat or prevent dysmenorrhea, and alleviate and prevent painful menstruation and symptoms such as nausea, fatigue, diarrhea, lower backache, and headache (col. 12, ll. 14-20).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Harrison et al. teach that symptoms such as headache as a result of dysmenorrhea are treated with their intravaginal drug delivery systems, but they do not teach using the instantly claimed anti-migraine or anti-nausea agents. However, Mahashabde et al. teach methods for treating migraine headaches through intravaginal delivery of selected serotonin reuptake inhibitors (SSRIs) to the systemic circulation (Abstract). Mahashabde et al. teach that the intravaginal delivery results in decreased

side effects due to decreased serum concentration and/or reduced first pass metabolism ([0028]). Mahashabde et al. further teach that the intravaginal composition may be formulated with a variety of pharmaceutical carriers, such as polyethylene glycols, amenable for administration as creams, gels, foams, tablets, suppositories and pessaries ([0034]). Also, Penkler et al. teach that anti-migraine drugs, such as sumatriptan, naratriptan, almotriptan, zolmitriptan, rizatriptan and eletriptan (col. 7, ll. 45-48), are suitable for delivery to the vagina, such as in the form of a suppository (col. 13, ll. 1-30). Therefore, it was well-known at the time of the invention to treat migraine headaches systemically through intravaginal application of anti-migraine drugs.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to administer an anti-migraine drug, such as sumatriptan, naratriptan, almotriptan, zolmitriptan, rizatriptan and eletriptan, intravaginally in the formulation of Harrison et al. because it was well-known at the time of the invention to treat migraine headaches systemically through intravaginal application of anti-migraine drugs.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants do not argue this rejection in their Request for Continued Examination filed 25 March 2009. Therefore, the examiner is responding to Applicant's Remarks filed 10 June 2008.

Applicants argue on pages 18-19 that Penkler et al. mandates formation of a neutral species by electrostatic attraction, whereas the instant invention uses a non-ionizable sorption promoter. However, the examiner respectfully argues that one of ordinary skill in the art at the time of the invention would have been motivated to treat migraine headaches through intravaginal administration to reduce side effects as a result of avoiding first-pass metabolism by the liver by avoiding the GI system, as taught by Harrison et al. and Mahashabde et al. Therefore, one of ordinary skill in the art would have been motivated to choose the anti-migraine drugs taught by Penkler et al., who also teach that the anti-migraine drugs can be administered intravaginally.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616